REMARKS

After amending the claims as set forth above, claims 1-5, 8-31, 33-35, 38 and 44-57 are now pending in this application. Claims 32 and 36 are canceled without prejudice or disclaimer and claims. Claims 8, 14, 30, 33, 35, 38, 44-50, 53 and 54 are amended. Claims 1, 3, 4, 5, 8, 18, 30, 35 and 49 are amended to recite that the pharmaceutical compositions are that is administered is an aerosol suitable for airway delivery. Support for this amendment that adds that the "pharmaceutical composition" is an "aerosol" is found in the specification on page 12, lines 25-26; page 18, lines 16-18 as well as the original claims. Applicants reserve the right to file the subject matter of any canceled claims or canceled subject matter in one or more continuing applications. Applicants include claims 8, 38 and 49 in this amendment and have removed the bracketed words in the set of clean claims above.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 14, 44-48 and 50

Claims 14, 44-48 and 50 are rejected as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention. Applicants respectfully traverse this rejection but in an effort to expedite prosecution and because the subject matter to delivery to blood vessel cells was canceled from the independent claims, reference to "an endothelial cell specific promoter" has been canceled from claims 14, 44-48 and 50. Withdrawal of this rejection is requested.

Claims 13, 14, 44-48 and 50

Claims 13, 14, 44-48 and 50 remain rejected as allegedly not enabled by the specification because the specification does not provide the description of the structure of such promoters, such as their nucleotide sequences and evidence that the members of a class of such promoter share a common structure. Applicants again respectfully traverse this rejection and as requested by the Examiner, applicants provided evidence that several

mammalian cell specific promoters were sufficiently well known in the art at the time of the present invention, and that these promoters were useful from expressing proteins in epithelial or muscle cells or in the lung airways of animals.

The Examiner states that he has considered applicants' arguments and the scientific publications that support applicants' position that mammalian cell specific promoters were well known in the prior art to persons skilled in the art at the time of the present invention but that he did not find them to be persuasive. Applicants believe that they have provided sufficient information through the use of scientific publications that were available to skilled persons in the art to support the subgenus of mammalian cell specific promoters, and more specifically epithelial cell specific promoters and smooth muscle cell specific promoters. These publication provide a representative number of mammalian cell specific promoters, such as epithelial cell specific promoters and a smooth muscle cell specific promoter that were available prior to and at the time of filing the provisional patent application upon which the present application claims priority.

For example, Exhibits 1 and 2, disclose an epithelial cell specific promoter, human cytokeratin 18 (K18), and disclose how to prepare constructs containing this promoter for the epithelial-specific expression of a transgene in the airway epithelia. Further Exhibits 3 and 4 show that the human surfactant Protein B promoter, also an epithelial-specific promoter that as characterized by the Examiner is only active in distal alveolar epithelium (type II cells), and also see, Exhibit 3, page 5, 1st col., lines 4-5, and bronchial tracheal epithelium (Clara cells). These two cell type are epithelial cells. Skilled persons in the art would know that these cells were epithelial cells.

In further support of this argument, also enclosed are two additional publications, one by Stripp *et al.*, *J.Biol. Chem.* 267:14703, published in 1992, identifying the promoter of the CC_{10} gene, a gene that is expressed in the epithelial cells, Clara cells, and a later publication by McGraw *et al.*, *Am.J. Physiol. Lung Cell Mol.Physiol.* 279: L379-L389 (2000) using the CC_{10} gene promoter described in Stripp *et al.* to limit expression of the β_2AR in Clara cells in transgenic mice.

Further, the alpha actin promoter is mentioned on page 10, lines 22-24 of the present specification, as a promoter that was known and disclosed in McGraw *et al.* (1999),

also Exhibit 7. Exhibits 6 and 7, previously cited, disclose the use of this promoter to express a transgene in the smooth muscle cells of transgenic mice and cell cultures.

Applicants maintain that they have provided evidence that shows that several mammalian cell specific promoters were known and available and methods of obtaining these promoters and inserting them into cassettes or vectors to express transgenes in epithelial cells and smooth muscle cells were well known to persons skilled in the art prior to applicants invention.

As previously argued, the DNA sequences of many mammalian cell specific promoters have been described in many scientific publications, as evidenced by the several publications cited in support of applicants' position that prior to and at the time of applicants invention, skilled persons could select, prepare and transfect epithelial cells and smooth muscle cells and obtain expression of a transgene expressed under the control of these promoters.

Applicants believe that they have provided sufficient evidence to support their position that the mammalian cell specific promoters were well known by persons in the art. Applicant again submits that a "patent need not disclose, and preferably omits, what is well known in the art." *Hybritech v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986). In view of the above information provided regarding the what is known by persons skilled in the art, it is requested that this rejection be withdrawn.

Claims 1-5, 8-38 and 44-50

Claims 1-5, 8-38 and 44-50 remain rejected as allegedly not enabled by the specification because the Examiner alleges that the application is not enabled for the treatment of diseases obviously including asthma as claims 55-57 also are rejected. Applicants respectfully traverse this rejection.

The Examiner states that he has considered Dr. Cornett's declaration but that it is insufficient to overcome the rejection of claims. The Examiner states that the claims are allegedly not enabled because the evidence presented does not demonstrate that any β_2AR was expressed *in vivo*. The Examiner is concerned whether the β_2AR may be expressed appropriately or expressed at a physiologically effective level, particularly for treating an

airway disease, such as asthma. The Examiner further states that the rats that were used in Dr. Cornett's experiments were not suffering from an airway disease. Further, the Examiner states that the evidence relies on inference from a qualitative assessment, and shows now physiologically relevant expression and activity of β_2AR.

Applicants respectfully take issue with the Examiner's assessment of the relevance of the data generated by Dr. Cornett's data provided in his declaration. The data from the rats showed that GFP was expressed in rats that were treated with both recombinant AAV cassettes and not in the control rats. In addition, direct evidence of co-expression of both β_2AR and GFP genes under the control of the CMV promoter (as constructs as used to transfect the rat lungs) in cultured epithelial cells (HEK293 cells) that β_2AR density was expressed 11-fold more than in control cells.

In further support of the McGraw publications (2000, attached herewith) and the previously cited McGraw publication (1999- Exhibit 7) show that a β_2AR construct was expressed in transgenic mice and the expression in the airway epithelial cells decreased bronchoconstruction.

The claims require the expression of β_2AR in airway cells. The more β2ARs present in the cells of the subject's airway, the more binding of β_2-agonists. In view of these arguments, applicants maintain that the amended claims are supported by the specification.

It is requested that the Examiner consider the attached declaration and accompanying figures supporting the expression of β2ARs in cells of the rat lung.

The publication from successful studies in March 2000, at Children's Hospital in Philadelphia and Stanford University reporting success in using gene therapy to treat hemophilia B in 3 patients and the results of the Italian group reporting the correction of severe combined immunodeficieny (SCID) by gene therapy (Aiuti et al., Science 296:2410-2413, (2002)) **(Exhibit 9),** were discussed to show success in gene therapy.
In view of these arguments, it is requested that this rejection be withdrawn.

Rejections under 35 U.S.C. § 102 and 103

The Examiner has maintained the rejections of various claims under 35 U.S.C. §§ 102 and 103 over Bretin *et al.*, Kawahira *et al.- 1998*, Kawahira *et al.- 1999*, Drazner *et al.*, Maurice *et al.*, and Hammond *et al.* as evidenced by Ping *et al.* in view of any one of Kawahira *et al.*- 1999 ("Kawahira-99"), Kawahira *et al.*- 1998 ("Kawahira-98") or Maurice *et al.* ("Maurice"). The Examiner has maintained all of these rejections but states that if the claims are amended to recite an "aerosol," the prior are does not meet this physical limitation. In an effort to expedite prosecution, applicants have amended the claims to recite aerosol. In view the comments and the claims amendments, it is requested that this rejection be withdrawn.

CONCLUSION

Entry of the amendment is respectfully requested. Applicants have amended the claims to reduce issues on appeal and have not raised any new issues or amended the claims to require a further search. Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

Date May 15, 2003

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MARKED UP VERSION OF CLAIMS

8. (Amended) A method of treating a human subject having airway [or vascular] disease comprising:

(a) administering via airway treatment to at least one cell type selected from the group consisting of airway epithelial cells, airway smooth muscle cells and [and] a combination thereof, a first composition comprising a vector comprising a DNA sequence encoding a β_2AR operably linked to a promoter that is functional in at least one of said cells of said subject, under conditions whereby the DNA sequence encoding said β_2AR is expressed in at least one of said cells; and

(b) administering via airway treatment a second composition comprising at least one β_2-adrenergic agonist into said cells of said subject.

14. (Amended) The method of claim 13, wherein said mammalian cell specific promoter is [selected from the group consisting of] an epithelial cell specific promoter[, an endothelial cell specific promoter and] **or** a smooth muscle cell specific promoter.

30. (Amended) A pharmaceutical composition comprising a vector comprising a DNA sequence encoding a β_2AR operably linked to a promoter that is functional in at least one cell of the airways of a human subject, wherein said cell is selected from the group consisting of an airway epithelial cells, airway smooth muscle cells and a combination thereof; and a pharmaceutically acceptable carrier, wherein said pharmaceutical composition is **an aerosol which is** suitable for airway delivery to said subject.

33. (Amended) A kit for the treatment of a human subject having airway disease comprising:

(a) a first pharmaceutical composition comprising a vector comprising a DNA sequence encoding a β_2AR operably linked to a promoter that is functional in at least one cell of the airways of a human subject, wherein said cell is selected from the group consisting of an airway epithelial cells, airway smooth muscle cells and a combination

thereof; and a pharmaceutically acceptable carrier, wherein said first pharmaceutical composition is **an aerosol which is** suitable for airway delivery to said subject; and

(b) a second pharmaceutical composition comprising at least one β_2-adrenergic agonist and a pharmaceutically acceptable carrier, wherein said second pharmaceutical composition is **an aerosol which is** suitable for airway delivery to said subject.

35. (Amended) The kit of claim 33, , wherein said promoter is an inducible promoter, said kit further comprises:

(c) a third pharmaceutical composition comprising a hormone or pharmacological agent that induces said promoter to express said β_2AR in at least one of said cells, wherein said third pharmaceutical composition is **an aerosol which is** suitable for airway delivery to said subject.

38. (Amended) A kit for the treatment of a human subject having airway [or vascular] disease comprising:

(a) a first pharmaceutical composition comprising a vector comprising a DNA sequence encoding a β_2AR operably linked to a promoter that is functional in at least one cell of the airways of a human subject, wherein said cell is selected from the group consisting of an airway epithelial cells, airway smooth muscle cells and a combination thereof; and a pharmaceutically acceptable carrier; and

(b) a second pharmaceutical composition comprising a hormone or pharmacological agent that induces said promoter to express said β_2AR in at least one of said cells, wherein said first and second pharmaceutical compositions are **aerosols which are** suitable for airway delivery to said subject.

44. (Amended) The method of claim 3, wherein said promoter is [a mammalian cell specific promoter selected from the group consisting of] an epithelial cell specific promoter[, an endothelial cell specific promoter and] **or** a smooth muscle cell specific promoter.

45. (Amended) The method of claim 5, wherein said promoter is [a mammalian cell specific promoter selected from the group consisting of] an epithelial cell specific

promoter[, an endothelial cell specific promoter and] **or** a smooth muscle cell specific promoter.

46 (Amended) The pharmaceutical composition of claim 30, wherein said promoter is [a mammalian cell specific promoter selected from the group consisting of] an epithelial cell specific promoter[, an endothelial cell specific promoter and] **or** a smooth muscle cell specific promoter.

47. (Amended) The kit of claim 35, wherein said promoter is [a mammalian cell specific promoter selected from the group consisting of] an epithelial cell specific promoter[, an endothelial cell specific promoter and] **or** a smooth muscle cell specific promoter.

48. (Amended) The kit of claim 38, wherein said promoter is [a mammalian cell specific promoter selected from the group consisting of] an epithelial cell specific promoter[, an endothelial cell specific promoter and] **or** a smooth muscle cell specific promoter.

49. (Amended) A kit for the treatment of a human subject having airway [or vascular] disease comprising:

a first pharmaceutical composition comprising a vector comprising a DNA sequence encoding a β_2AR operably linked to a promoter that is functional in at least one cell of the airways of a human subject, wherein said cell is selected from the group consisting of an airway epithelial cells, airway smooth muscle cells and a combination thereof; and a pharmaceutically acceptable carrier;

a second pharmaceutical composition comprising at least one β_2-adrenergic agonist and a pharmaceutically acceptable carrier; and

a third pharmaceutical composition comprising a hormone or pharmacological agent that induces said promoter to express said β_2AR in at least one of said cells, wherein said first, second and third pharmaceutical compositions are **aerosols which are** suitable for airway delivery to said subject.

50. (Amended) The kit of claim 49, wherein said promoter is [a mammalian cell specific promoter selected from the group consisting of] an epithelial cell specific promoter[, an endothelial cell specific promoter and] **or** a smooth muscle cell specific promoter.

53. (Amended) The [method] **pharmaceutical composition** of claim 31, wherein said modified β_2AR possesses at least one property selected from the group consisting of increased responsiveness to β_2AR agonists, increased affinity to β_2-adrenergic agonists, and capability to increase the potency of β_2AR agonists to stimulate downstream signal transduction pathways, as compared to the native β_2AR.

54. (Amended) The [method] **pharmaceutical composition** of claim 53, wherein said modified β_2AR is modified from the native β_2AR by the deletion of amino acids, substitution of amino acids, replacement of amino acids or a combination thereof.